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THE PRINCIPLES OF NEUROMUSCULAR BLOCK*

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NEUROMUSCULAR block, in the old sense of the term, created by Claude Bernard, could be briefly and almost completely described as that state of a nerve muscle preparation in which stimulation of a motor nerve failed to elicit a contraction of its muscle, although conduction along nerve and direct excitability of muscle were unimpaired. But the interest in curare, and the exploitation both of curare alkaloids and of substances related to it, has brought to light many other features important both for clinical practice and scientific theory. The simplest way of describing these is by proceeding at once to a comparison of the actions of two particular compounds, d-tubocurarine and decamethonium; the contrast in their effects illustrates admirably the complexity of the events now known to be involved in neuromuscular transmission and its paralysis. The comparison is summarised in Table I, and illustrated in Fig. I.

Comparison Between the Characteristics of Neuromuscular Block by D-Tubocurarine and by Decamethonium

1. *Variations in muscle sensitivity*

Muscles differ considerably in their sensitivity to paralysis by these blocking agents. In man the ocular, facial, laryngeal, and pharyngeal muscles, together with those of the hand, are particularly sensitive to a drug such as d-tubocurarine. After further doses the major supporting muscles of the limb, the trunk muscles and the respiratory muscles are attacked. Decamethonium produces a similar picture, but for an equal weakness of the hand and limb muscles there is less weakness of the facial and pharyngeal muscles. In animals a difference between the two drugs becomes even more striking. In the cat the red postural muscle, soleus, is particularly sensitive to d-tubocurarine, while the white quickly-contracting muscle, tibialis, is less sensitive. For decamethonium on the other hand this relationship is exactly reversed, and it is tibialis which is particularly affected. Again, one finds, on comparing different species, that, whereas the rat is outstandingly sensitive to d-tubocurarine and the mouse, rabbit and cat progressively less sensitive, for decamethonium the rat is outstandingly resistant and the order mouse-rabbit-cat is that of progressively increasing sensitivity.

*This is the first of a series of articles kindly written for *Anæsthesia* by invitation.

TABLE I

Test	d-tubocurarine	Decamethonium
Sensitivity of different species.	Man and cat < rabbit < mouse < rat	Man and cat > rabbit > mouse > rat
Sensitivity of different muscles within one species		
cat:	Respiration and soleus > tibialis	Respiration and soleus < tibialis
man:	laryngeal, pharyngeal, and ocular muscles outstandingly sensitive compared to skeletal muscles	laryngeal, pharyngeal, and ocular muscles only moderately sensitive, compared to skeletal
Incidence of stimulant effects on muscle	Nil or trivial in all species tested*	Spontaneous fasciculations* Repetitive response by muscle to single nerve shocks* Contracture of frog muscle, avian muscle, denervated cat muscle. Rapid twitch of cat muscle to intra-arterial injection. Activation of muscle spindles
Effect of substances raising threshold of endplate to acetylcholine:		
d-tubocurarine, gallamine, etc.	Synergism*	Antagonism*
hexamethonium, etc....	Potentiation*	Antagonism*
ether and cyclopropane	Potentiation (up to 40%)*	Antagonism*
Effect of other drugs producing stimulant effects (acetylcholine etc.)	Antagonism*	Synergism*
Tension *during* a tetanus	Rapid waning*	Well sustained*
Miscellaneous:		
anticholinesterases	Antagonism*	Little effect, occasionally feeble potentiation or antagonism*
Tensilon	Antagonism*	No effect or potentiation*
Phenol	Antagonism	No effect
Previous tetanisation	Antagonism	No effect*
Potassium	Antagonism	No effect
Activity in myasthenia	Hypersensitivity* (up to 10-fold)	No hypersensitivity; sometimes 3-fold tolerance; initial strengthening action*
Potential change at endplate	None	Depolarisation
Anode or Cathode applied to endplate	Anode intensifies. Cathode relieves	Anode relieves. Cathode intensifies

< = " less sensitive than ", > = " more sensitive than ".
Tests marked with an asterisk could be used in the human subject.

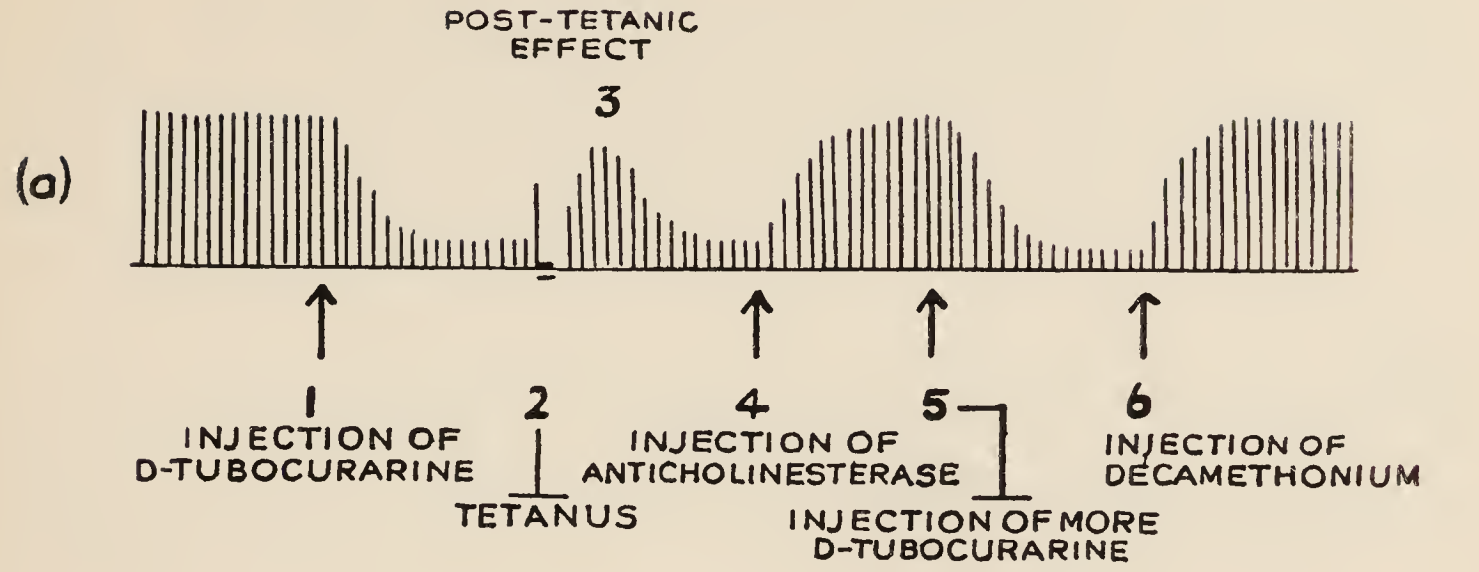


FIG.1.—Diagram summarising some of the contrasting features of competitive and depolarising block. The vertical lines represent twitches of a cat muscle to single shocks every 10 seconds. In (*a*) d-tubocurarine is injected at (1); in (*b*) decamethonium (followed by spontaneous fasciculations). Then may be seen at (2) the character of a tetanic contraction; at (3) the after effects of this; at (4) the effect of an anticholinesterase; at (5) the effect of an injection of d-tubocurarine; at (6) the effect of an injection of decamethonium.

It would be impossible to make such a tracing in practice, because the time relationships are grossly distorted. But all the individual parts of it have been obtained.

There is, in short, an inverse relationship between the drugs, such that when one muscle is relatively susceptible to one of the two drugs, it tends to be relatively resistant to the other, and *vice versa*.

2. The onset of block with d-tubocurarine is always smooth. With decamethonium on the other hand, there are always preliminary vestiges of stimulant action, such as fasciculations of the limb muscles or of the face before the paralysis sets in. With succinylcholine this may be quite vigorous. In animals the stimulating action may cause a repetitive response of a muscle to single nerve shocks; or (if decamethonium is injected intra-arterially) a rapid twitch of normal muscle; or contractures of frog, avian, or denervated mammalian muscle.

3. The compounds contrast in their interactions with substances which raise the endplate threshold to acetylcholine. The previous administration of d-tubocurarine or similarly-acting substances; or hexamethonium and other ganglion blocking agents; or ether or cyclopropane anæsthesia, potentiates d-tubocurarine but lessens the action of decamethonium.

4. The two drugs contrast again, but in the opposite way, in their interactions with substances stimulating the endplate, such as acetylcholine, succinylcholine, or decamethonium itself. If these are given during a block produced by d-tubocurarine, the block is lessened, but they increase the block due to decamethonium.

5. The curarised muscle finds it difficult to sustain a tetanic contraction; the typical response is of a good initial twitch, which then fades away to end as quite a feeble maintained contraction, or none at all. The cause of this is not established, but a contributory element is probably the waning of acetylcholine output from the motor nerve terminals during rapidly repeated stimulation. This will lead to a rising ratio of curare to acetylcholine, and thus increase the intensity of the competitive block. With decamethonium, however, the tetanic contraction is well sustained throughout its course.

6. D-tubocurarine block is susceptible to antagonism by a considerable number of agents, in addition to the muscle stimulating drugs already mentioned. These are (1) anticholinesterases, which, by preserving acetylcholine at the neuromuscular junction, allow it to reach a higher concentration after each nerve impulse, so that it is more likely to have an effect at the curarised endplate. (2) Tensilon and similar drugs. (3) Phenol. (4) Previous tetanisation of the muscle. (5) Potassium. But none of these agents antagonise decamethonium; and some of the anticholinesterases and Tensilon may actually increase its action.

7. In the myasthenic, d-tubocurarine is much more effective than normal, and as little as 1–2 mg. may produce a considerable effect. But decamethonium is no more effective than in the normal; sometimes, in fact, the subject is actually resistant to it; in some cases, too, a transient strengthening of certain muscles may be seen just after decamethonium has been given.

These differences may be summed up in three statements:

(*i*) Neuromuscular block by decamethonium is associated with an initial stimulant action; this is absent with d-tubocurarine.

(*ii*) There is an inverse relationship between the conditions which favour the action of d-tubocurarine and those which favour decamethonium.

(*iii*) The action of d-tubocurarine can be fairly readily deepened or lightened (*e.g.*, by tetanisation, anticholinesterases, etc.) and may be termed *labile*; that of decamethonium is harder to modify, and may be called *stable*.

To account for these characteristic differences of behaviour it is necessary to digress briefly, so as to analyse more closely the physiological elements involved in the activity of nerve and muscle, and in the synapse between them. We shall consider in turn the propagated response, the mechanism of neuromuscular transmission and the local response; from the properties of these responses, many of the peculiarities of blocking drugs can then be seen to follow logically.

The " Propagated " Response of Muscle and Nerve

The nerves and muscles in the body have, amongst other faculties, the property of transmitting rapidly along their lengths, a wave of excitation which in nerve serves for the transmission of signals throughout the body, and in muscle serves to initiate and synchronise the activity of the contractile material in the muscle fibre. This excitatory wave depends for its initiation and movement on the fact that the surface membranes of nerve and muscle fibres are electrically charged. The " membrane potential " is such that the outside is positive to the inside by about 1/10th volt. (c.f. Fig. 2d). If this membrane potential is reduced sufficiently at a particular point (a process called " depolarisation " because it removes the polarity, +ve outside, −ve inside, of the membrane), the membrane becomes activated; and by flow of electric current outside the fibre into the depolarised region, the adjacent normal membrane is in turn depolarised and activated. Thus the wave of depolarisation spreads like the ignition of a train of gunpowder, each piece of the fibre exciting the next. The depolarisation is transient, and the membrane potential at a given point rapidly returns to its normal value. The total picture is, therefore, of a transient wave of negativity (the " action potential ") flashing away along the fibre from the point of initiation of the depolarisation.

The depolarisation required to start the process in a given stretch of nerve or muscle fibre may be due to an injury or an action potential in the adjacent membrane; other means are by discharging the membrane with external electrodes, as used in ordinary electrical excitation, and by chemical depolarising agents such as potassium or acetylcholine. All these are electrically equivalent in that they produce a local reduction of the potential across the membrane.

Recent work on the action potential, using internal electrodes, has made our picture of its movement more precise, by determining (for instance) how much a membrane must be depolarised in order to change from its resting to its active state, and how far ahead an

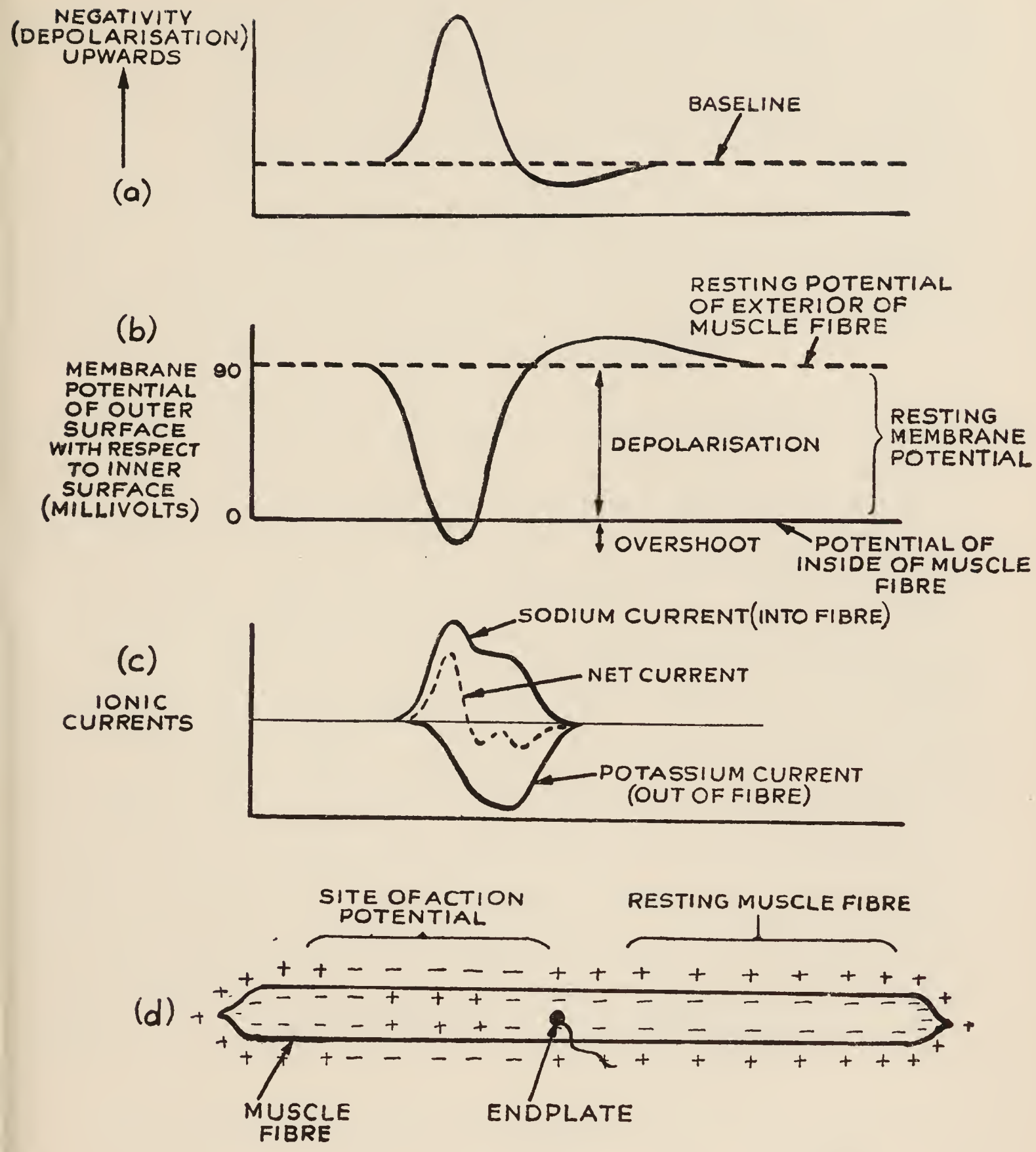


FIG. 2.—Diagram of events during a propagated action potential:
(*a*) Action potential conventionally recorded with negativity upwards.
(*b*) Action potential as recorded with one electrode inside the muscle fibre, showing the resting membrane potential and the "overshoot".
(*c*) The ionic currents during an action potential.
(*d*) Highly diagrammatic representation of disposition of electric charge about resting membrane (to the right of endplate) and about active membrane (to the left of the endplate). With normal transmission, action potentials pass in *both* directions outwards from the endplate.

action potential can stir resting membrane to activity. But it has also shown that the membrane, as the wave of propagated excitation traverses it, undergoes subtler changes than previously suspected; not only does the potential across it disappear—it actually reverses or " overshoots ". Fig. 2b shows the situation diagrammatically. It may be noted that the main " spike " of the action potential in the diagram is downward, *i.e.*, inverted from the conventional record. This need not be confusing; the conventional recording procedure, in which leads from the outside of the fibre are taken, and in which the negativity of the excited membrane is recorded upwards (Fig. 2a), simply springs from the usual tendency in any visual representation to register activity upwards.

The discovery of the " overshoot " of the action potential was the first step in work that has transformed our notions of the propagated excitation wave in nerve and muscle. It has shown, for instance, that although the concentration of sodium ions in the interstitial fluid does not affect the *resting* membrane potential, it influences profoundly the *action* potential; the latter is reversibly abolished if the external sodium is reduced sufficiently far. The old model of excitation, as simply a more or less complete depolarisation of the fibre membrane, has been replaced by another in which the membrane (if depolarised by some stimulus to a certain rather critical threshold level), exchanges its relative impermeability to sodium when resting, for a specifically high permeability to sodium during excitation. The vigorous flux of sodium ions produces the complete membrane depolarisation and then the " overshoot ", and a subsequent movement of potassium ions in the opposite direction then restores the membrane potential and quenches the excitation (Fig. 2c). In contrast to the old view of the simple collapse of an ionic impermeability, the fundamental process now appears to consist of a switch from the vigorous exclusion of sodium ions during rest (the so-called " sodium pump ") to an actual facilitation of their entry through the fibre membrane, during the initial part of the action potential.

Neuromuscular Transmission and the " Local " Response

Neuromuscular transmission involves a new factor, that of bridging a distinct (though narrow) anatomical gap between the nerve endings and the muscle fibre; and there has turned out to be an additional element involved. It was discovered by electrical recording that during activity not only the nerve action potential and the muscle action potential, but a third phenomenon, the " endplate potential " could be detected.

The Endplate Potential.—It received this name because it is a potential change which (unlike the other two) is restricted to the endplate region. It is a relatively small potential when recorded with external electrodes, and is usually swamped by the much larger

muscle action potential; special procedures are used to reveal it, of which the simplest, and commonest, is curarisation of the muscle.

The discovery of the endplate potential led to the generally accepted view that transmission takes place in the following sequence: propagated nerve impulse → local endplate potential at endplate region of muscle fibre → propagated muscle action potential. It changed the problem from that of how the nerve impulse elicits a muscle action potential, to that of how it elicits this special localised potential; and it placed a most valuable and much used tool at the investigator's disposal, with which if he wishes he can study the action of ions or drugs on the transmission process without the complication of the superimposed muscle action potential. But it did not, in itself, prove either of the two theories of transmission then current, that of transmission by a chemical agent, and that by electrical means.

The structure of the endplate has naturally received a good deal of attention. Its precise anatomy is still not entirely clear but the main points (represented diagrammatically in Fig. 3) seem to be first that there is a distinct gap between the nerve terminations and the muscle fibre membrane beneath them: second that the muscle membrane below the nerve terminals is specialised, possessing what Couteaux describes as a " palisade " structure. The nerve endings rest in a specialised bed of glial tissue, which may have important nutritional functions; and there is a very high concentration of cholinesterase in the region. (See glossary for discussion of meanings of the words " endplate " and " nerve ending ").

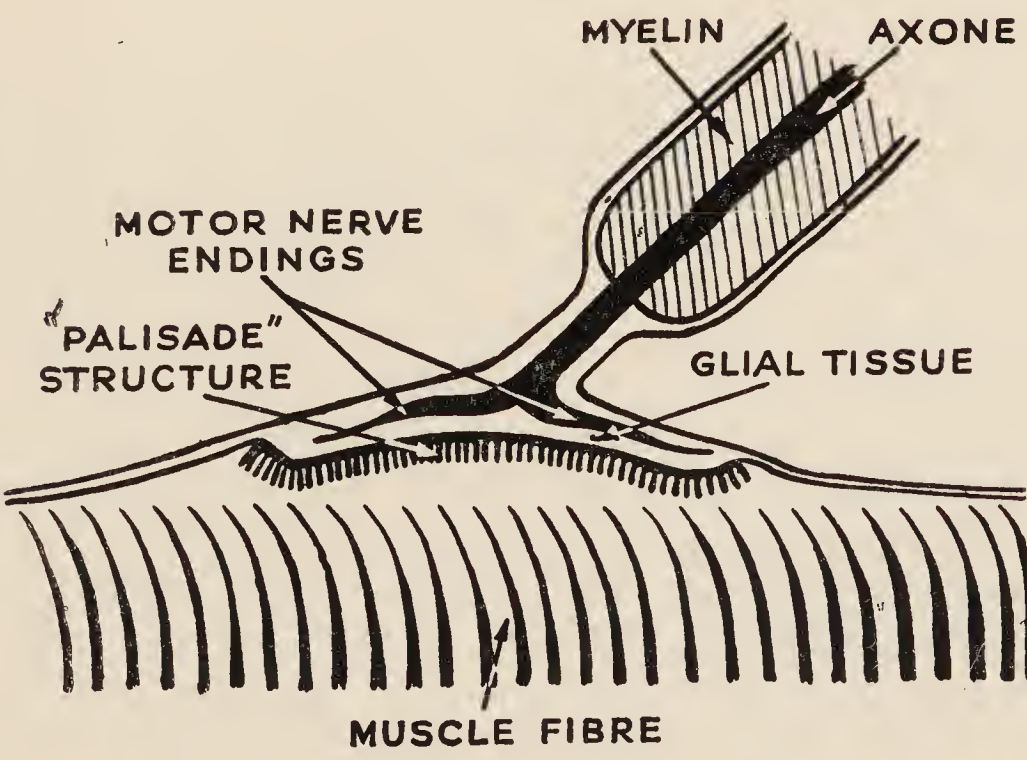


FIG. 3.—Diagrammatic representation of motor nerve-ending, endplate, and upper half of a muscle fibre.

Mechanism of Transmission.—Neuromuscular transmission is now generally admitted to be mediated by a particular chemical substance, acetylcholine. The proof of this was primarily by pharmacological and electropharmacological experiments. In brief, the evidence consists of the following:

(*a*) a substance—specifically identified as acetylcholine—is released at motor nerve terminals when these nerves are stimulated;

(*b*) this substance is capable of exciting muscles directly in small amounts.

(*c*) acetylcholine can produce a specific depolarisation of the endplate region, capable of initiating a normal propagated response in the muscle fibre;

(*d*) there is an enzyme, cholinesterase, localised precisely at the endplate region which is specifically active in destroying acetylcholine;

(*e*) drugs which inhibit cholinesterase also interfere in the expected way with neuromuscular transmission;

(*f*) drugs chemically related to acetylcholine interfere with transmission.

A discussion of all the experimental details concerned need not be pursued here; but it is worthwhile pointing out that the evidence referred to in (*f*) alone provides overwhelming support for the idea that acetylcholine or some very similar substance transmits excitation across this synapse. The enormous range of salts of quaternary nitrogen capable of activity at the neuromuscular junction would be quite inexplicable were excitation actually transmitted by electrical means.

But to all this has been added recently the admission by electrophysiologists that electrical processes are actually inadequate for the task. In the first place it has been shown that there is, in the initiation of the first depolarisation of the endplate region produced by a nerve impulse, a brief latency of a fraction of a millisecond which cannot be accounted for on electrical grounds; yet it is easily explicable if the time for the release and action of acetylcholine is taken into account. It is ironical that whereas in the early debates it was argued that transmission by acetylcholine would be too slow to account for the rapidity of normal transmission, now it is necessary to invoke chemical transmission to account for its slowness. Secondly it has been concluded that the electrical potentials available from the motor-nerve terminals would be quite inadequate to excite the motor nerve endplate electrically, so that it has become necessary to seek some other source of electrical energy, such as is available if a chemical compound is released.

The release and action of acetylcholine.—We are still somewhat in the dark as to how acetylcholine is released. It is known that sodium ions are required for release to take place; and calcium deficiency prevents release. It is possible that when the nerve action potential reaches the nerve terminals it there releases acetylcholine instead of potassium in exchange for the sodium which enters during activity. But other theories have been canvassed.

More important for the present discussion is the action of acetylcholine after release. We now know that its appearance and rapid hydrolysis by endplate cholinesterase cause the transient endplate potential; and further that (1) this response is not propagated, (2) it is not all-or-none but can vary continuously over a wide range, according to the amount of acetylcholine applied to the endplate, from no action to that required to "trigger off" the action potential. We also know that (3) sodium ions are not necessary for depolarisation of the endplate by acetylcholine, and (4) that the depolarisation is only partial. It has been estimated that the amount of acetylcholine released is too small itself to carry the electric charge required to produce the endplate potentials observed, so that it cannot be supposed that the depolarisation is produced simply by the entry of acetylcholine ions rapidly across the muscle membrane. The precise mechanism of depolarisation is in fact still unknown; it has been compared to a "short-circuiting" of the membrane, of the same kind as in the old theory of propagation along muscle and nerve.

There are two other features to be mentioned which link up with work many years ago on the phenomenon known as "contracture". When acetylcholine is applied to certain kinds of muscle (particularly frog and fowl muscle), it produces a *sustained* shortening of the muscle, localised to the point of application, which is associated with a sustained depolarisation, and with the development of electrical inexcitability. This type of shortening of a muscle, in which no propagated contractions could be recorded, was termed a "contracture" in contrast to the "contraction" of muscle mediated by propagated muscle activity. The action of acetylcholine at the mammalian endplate is precisely analogous to it but without the mechanical effect; although the endplate potential is normally transient, this is only because of the cholinesterase there, and when the enzyme cannot act (for one reason or another) acetylcholine then produces a persistent depolarisation, and the endplate becomes electrically inexcitable. This inexcitability does not develop immediately; so that a common result of producing a "local" response in a muscle is the initiation of one or more "propagated" responses along the fibre, during the early stages of the response. The events of muscular transmission are, in fact, those where a "contracture" has been initiated at the endplate and then quenched (by action of cholinesterase) after one propagated response has been evoked.

There are, therefore, several interchangeable idioms with which the events of neuromuscular transmission can be described. One may say that the release of acetylcholine by the *action potential* in the nerve produces an *endplate potential* which evokes an *action potential* in the muscle fibre; or one may say that the *propagated* response of nerve by means of the electromotive power of acetylcholine elicits a *local* endplate response which then arouses a *propagated* response of muscle; or one could say (stretching the point somewhat) that a "*contraction*" of nerve (or at least its electrical counterpart) excites a "*contracture*" of the endplate region followed by a "*contraction*" of the muscle.

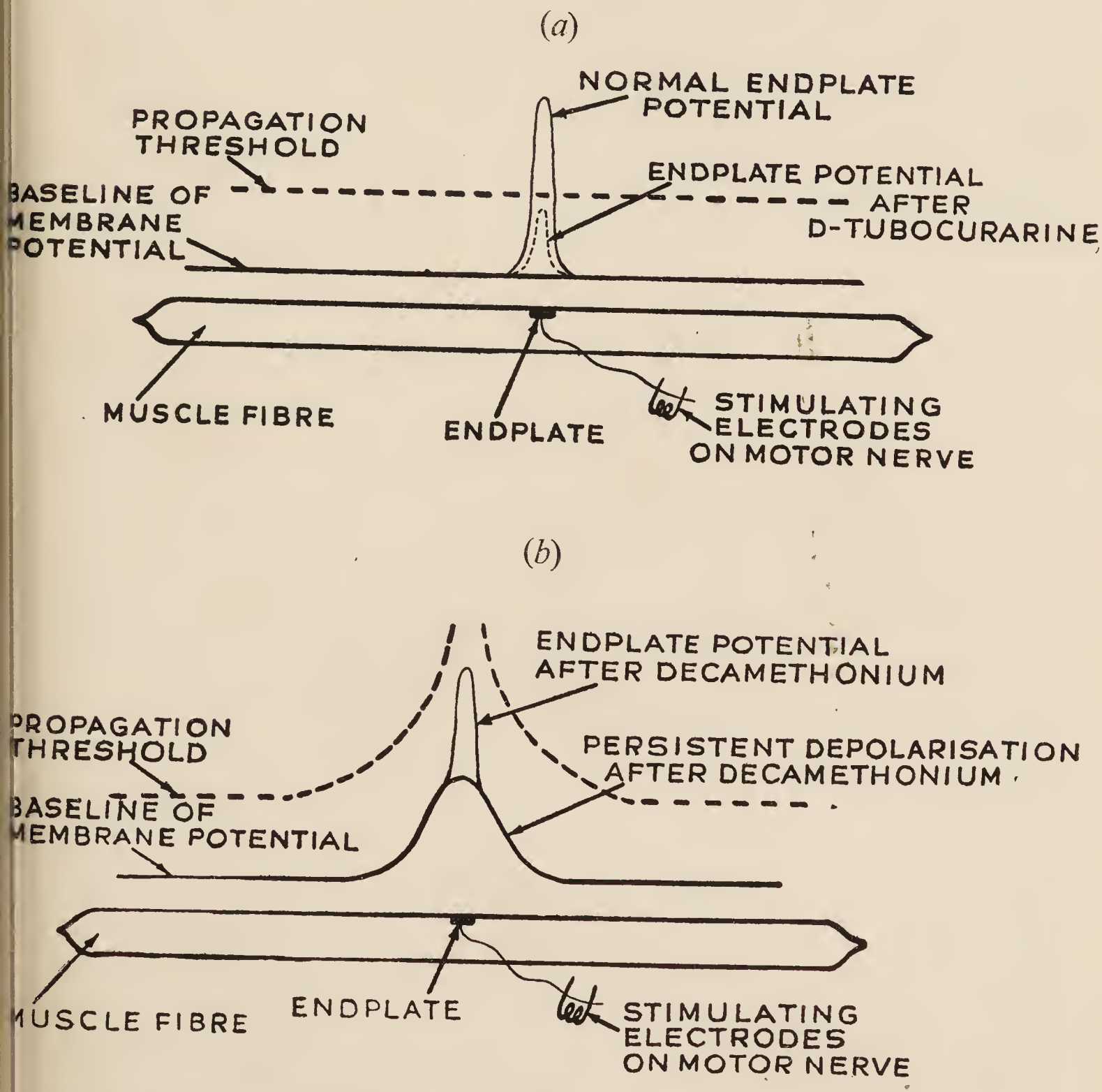


FIG. 4.—Diagrams of the distribution of potential along muscles treated with (*a*) d-tubocurarine and (*b*) decamethonium. The thick continuous line shows the baseline and persisting depolarisation (if present); the thin lines show the peaks of endplate potentials, in response to nerve stimulation.

Mechanisms of Neuromuscular Block

It is now straightforward to account for the two main types of neuromuscular block.

(*a*) *Competitive Neuromuscular Block*.—This, produced typically by d-tubocurarine, is due simply to the ability of the blocking agent to lessen the effectiveness of acetylcholine at the endplate. It is supposed that these drugs acting in this way (almost invariably salts of quaternary nitrogen) are sufficiently like acetylcholine to have some affinity for its receptor sites but sufficiently unlike to be incapable of initiating the process of depolarisation. They thus "compete" for receptor sites with acetylcholine, and so render a given quantity of the latter less active than normally. The endplate potential aroused thus comes to fall short of the amount needed to activate the adjoining muscle membrane, *i.e.* to fall short of the "propagation threshold" (Fig. 4a). Such drugs also antagonise acetylcholine's contracture-producing activity on frog and fowl muscle. Their action is precisely analogous to many other pharmacological antagonisms, such as that of hexamethonium at the ganglionic synapse, atropine at the peripheral cholinergic synapse, or of antihistamines against histamine.

(*b*) *Depolarisation block*.—Block of a different kind may be produced by drugs which have a rather closer relationship to acetylcholine, so that they can actually initiate the depolarisation process. Decamethonium, acting on human, feline or avian muscle, provides a prototype of such an action. It can depolarise the motor endplate in doses almost as small as those in which acetylcholine may act, but, unlike acetylcholine, the compound cannot be hydrolysed, so that the depolarisation produced persists not for milliseconds but for minutes or even hours, and comes to spread a little way into the adjacent muscle membrane. Under these circumstances the initial enhanced excitability of the endplate region, which may even go so far as causing momentarily the initiation of propagated impulses in the muscle fibre, passes over into an inexcitability. In the fibre, with its chronically depolarised endplate, we now find that the whole endplate region has become much more difficult to excite by electrical stimulation; it provides an inexcitable barrier to the passage of a directly stimulated muscle action potential along the muscle fibre, and if an endplate potential is set up it has to be much bigger than usual if it is to succeed in stimulating the fibre as a whole. The electrical inexcitability of the endplate region and of the immediately adjacent membrane in fact has become so great that even though an endplate potential may be set up at the endplate region, and sums with the endplate depolarisation already present, yet the sum of these two potentials is still not great enough to excite the muscle fibre, so that block occurs. (Fig. 4b). A particularly interesting fact is that by removing the depolarisation electrically (by applying an anode to the endplate) the block is also removed; and a cathode applied

to the endplate will deepen the block. This is the exact opposite of the situation with d-tubocurarine, when an anode (which now hyperpolarises the endplate) increases block, and a cathode (by helping depolarise the endplate) may reverse it—temporarily at any rate. Block of this sort in peripheral nerve is in fact familiar to physiologists under the term " cathodal block ", where it has long been known that prolonged and vigorous excitation may lead to a similar condition of electrical inexcitability. It may be compared, somewhat crudely, to a refractoriness following overstimulation; or likened to that fable in which by crying " Wolf! Wolf! " too often, the shepherd boy rendered his hearers inexcitable and blocked the propagation of what was (at last) a genuine motor impulse (Aesop et al; 600 B.C.)

The question has been raised whether a persistent endplate depolarisation is " unphysiological " and likely in itself to be dangerous to the body. There is no reason to suppose that this is true. A far more extensive depolarisation of the whole length of the muscle fibres of the body takes place during any vigorous muscle contraction; yet long maintained muscular activity is harmless or beneficial. No evidence exists that prolonged exposure to decamethonium (or for that matter to a competitive drug, if free of side effects) is harmful. It seems that neither over-stimulation nor under-stimulation of the endplate damages it, provided that the organism as a whole is protected from asphyxia.

We are now in a position to interpret, in part at least, the differences in behaviour between d-tubocurarine and decamethonium.

(1) *The stimulant action* which decamethonium possesses and which d-tubocurarine lacks is obviously related to the endplate depolarisation produced by the former. The initial effects of depolarisation by decamethonium, before endplate inexcitability has set in, are simply those of an excitation of muscle, analogous to that of voluntary activity, but of course far less well synchronised.

(2) *The inverse relationship* between the conditions of sensitivity between the two drugs is likewise inevitable. For a procedure which raises the threshold to acetylcholine (and hence sensitises to d-tubocurarine) must also raise the threshold to other depolarising agents and hence lessen the chances of their producing a depolarisation sufficient to induce endplate inexcitability. Conversely, if depolarisation of the endplate is favoured so that the latter compounds act more effectively, less acetylcholine is needed to produce a given endplate potential, and curare will act at a relative disadvantage. (It must be admitted at the same time, however, that the question why, for instance, such variations in sensitivity of different muscles and of different species occur, remains a fascinating but unanswered problem).

(3) The relative *stability* of decamethonium block and the *lability* of d-tubocurarine block is a more complex question, beyond the

scope of this review. But the situation may be summarised by suggesting that, whereas with d-tubocurarine block the endplate response is brought on to the discriminating and sensitive part of its dose-response curve, with decamethonium the summation of the depolarisation which it produces itself with that of the released acetylcholine means that the total chemical excitation of the endplate must be nearly maximal and hence difficult to interfere with. Thus those procedures which slightly increase or lessen the endplate response to acetylcholine may readily antagonise or increase the action of d-tubocurarine, where the endplate response is well submaximal, but will be ineffective with decamethonium.

(*c*) *Mixed Block*.—With some drugs, and in some animals, the mechanism of the neuromuscular block produced by certain compounds does not fall clearly into either of the two categories described, but appears to represent an action corresponding to a mixture of the two. In this group of drugs with a mixed action the transition always seems to be in the direction from being initially like a depolarising drug to ending as a d-tubocurarine-like drug. There is no satisfactory explanation of this type of action, but it is fairly common in pharmacology, particularly among sympathomimetic amines. Thus ephedrine or ergotamine at first produces an adrenaline-like action which then wanes and is followed by an antagonism to adrenaline injected or released in the body.

It is uncertain how often mixed block occurs in practice. One obvious instance is when both a competitive drug and a depolarising drug are used in the same patient. Under such circumstances decamethonium begins to behave more and more like a competitive drug. A similar case occurs where decamethonium is administered to the myasthenic, when, in addition to being tolerated to a high degree, its properties become like those of d-tubocurarine. The general result, however, in all situations of this type will be that a depolarising drug will tend to lose its characteristic actions, show less initial stimulant effects, and come to be additive with competitive drugs and susceptible to anticholinesterases.

A mixed action of another kind exists in the compound Mytolon, in which a competitive action is combined with a significant anticholinesterase potency. This apparently imparts to it a few decamethonium-like characteristics, and diminishes, although it does not abolish, its sensitivity to anticholinesterases as antidotes.

(*d*) *Block by Deficiency of Transmitter*.—For the sake of completeness it is necessary briefly to mention a further means of interference with neuromuscular transmission. With competitive or depolarisation block acetylcholine release takes place normally, but the acetylcholine cannot produce its usual effect. But failure of transmission may also be brought about by preventing normal acetylcholine release. Botulinum toxin and procaine are believed to act in this way, and changes in ionic composition of fluid bathing the

muscle (low sodium, low calcium, high phosphate or high magnesium) have a similar effect.

Block of this kind at the neuromuscular junction is hardly of practical importance at present, for botulinum has an irreversible action, procaine has to be given in very large doses to exert any effect, and ionic changes of the magnitude required would be hardly compatible with life. But the possibility of a really active reversible inhibitor of acetylcholine release is not likely to remain unexplored for long.

Antagonists to Neuromuscular Block

(1) *Anticholinesterases.*—The mechanism of the antagonism, exerted only against competitive blocking agents, has already been considered. The antagonism by preservation of released acetylcholine is of course limited, and can go no further once the cholinesterase at the endplate is inhibited. But with neostigmine a further factor is involved, a direct decamethonium-like action at the endplate, from which derives a part of its usefulness as an antagonist. It seems rarely to be worthwhile to give large amounts of neostigmine, and there is some evidence that after it has exerted its anti-esterase action and its direct action, a large dose may then go on to produce neuromuscular block itself, for which (of course) no antidote is available, and which may be very prolonged. Given in reasonable dosage, however, it is still unrivalled as an antidote to d-tubocurarine and in the treatment of myasthenia gravis.

(2) *Tensilon and related phenyl-alkylammonium derivatives*, are in a slightly different category and probably possess at least three properties: (1) a moderate anticholinesterase action; (2) a direct endplate stimulating action; (3) an ability to sensitise the endplate to depolarising drugs (the mechanism still being obscure). Their action is transient, and large doses themselves induce neuromuscular block.

(3) It is important to remember, when several drugs have been administered to a patient, that they may have some mutual antagonism to each other. Ether and cyclopropane, or hexamethonium, given in the presence of a depolarising drug are typical examples. Hexamethonium has not proved to be of any value in antagonising decamethonium in man; but it is worth noting that in poisoning with anticholinesterases (in which death may be due in part to depolarisation block by acetylcholine preserved at the endplate) hexamethonium has a considerable protective effect, sometimes greater than that of atropine, and synergising strongly with it.

The General Properties of a Quaternary Salt

All the drugs which compete with or mimic acetylcholine at all closely, resemble it in chemical structure. This has important consequences for the way such drugs are handled by the body and for their sideactions.

(*a*) *Distribution.*—Quaternary salts are all very strong bases, completely ionised. This means that although they can pass endothelial filters, such as capillary walls, glomerular membranes, and across the placenta, they will only with difficulty traverse the cellular barriers of the body; for it is only in the unionised form that a base can enter a cell at all rapidly. Three examples illustrating this can be chosen:

1. All the quaternary muscle relaxants are relatively inactive by mouth, because of the cellular barrier presented by the intestinal mucosa.

2. Although d-tubocurarine and other related substances are convulsant when applied directly by cisternal or ventricular injection to the C.N.S., such effects are never normally seen with systemic administration; even when large doses are given the blood-brain barrier proves impenetrable to their quaternary molecules.

3. The curare alkaloids and their synthetic counterparts are for the most part excreted as such in the urine, and are little or not detectably metabolised; this may be regarded as a consequence of their inability to penetrate cells and hence their failure to reach the enzymes which might destroy them.

(*b*) *Relationship to other actions of acetylcholine.*—Acetylcholine is involved in transmission of nervous effects at three sites outside the C.N.S., (1) the parasympathetic endings, and the sweat glands, (2) the ganglia, and (3) the neuromuscular junction. Now, a relationship to acetylcholine may show itself in one of three ways; a drug may (*a*) imitate acetylcholine; (*b*) competitively block it; (*c*) inhibit the enzyme destroying it. We thus have 9 types of action centred round acetylcholine; a drug may mimic, block or preserve the transmitter at any of three synapses. All these actions are liable to be displayed in widely different proportions by different substances. It becomes necessary, therefore, in studying the properties of neuromuscular blocking agents, to be prepared for such additional actions; they are in fact quite common, but usually in a degree sufficiently slight to be negligible clinically. The ganglion-blocking property of d-tubocurarine, the ganglion stimulating action of succinylcholine, and the antiesterase action of Mytolon are the most important examples in the present context.

Histamine Liberation

Many bases used in medicine (such as morphine, pethidine, atropine, the trypanocidal diamidines) can release into the circulation the histamine which is normally held by the tissues in some unknown but inactive form. In the dog, heparin is also released, so that the blood clots less readily. The quaternary salts are not, in general, particularly active in this respect, but d-tubocurarine is an exception. Treatment of tetanus provides a very severe test of freedom from

toxicity; and the vascular effects of released histamine probably account for the failure of d-tubocurarine to relieve the spasms safely in this disease. There is also a suggestive incidence of cases of bronchospasm with d-tubocurarine to which histamine-liberation may well have contributed. It must be supposed that only occasional subjects are susceptible, just as morphine is liable to have a lethal action in a case of bronchial asthma. It should be noted that antihistamines are generally rather ineffective against the effects of histamine liberators.

Mytolon and Laudolissin also have significant histamine liberating power. Succinylcholine is not very active in this respect, but the large doses of it now given sometimes (in prolonged infusions) may well enable histamine release to occur, although there is no clinical suspicion of it yet.

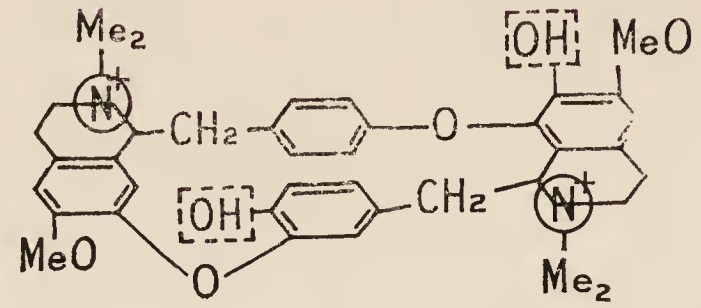
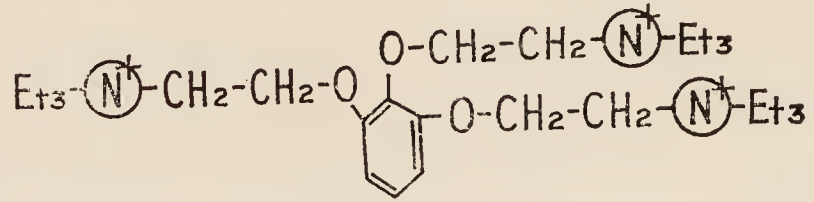
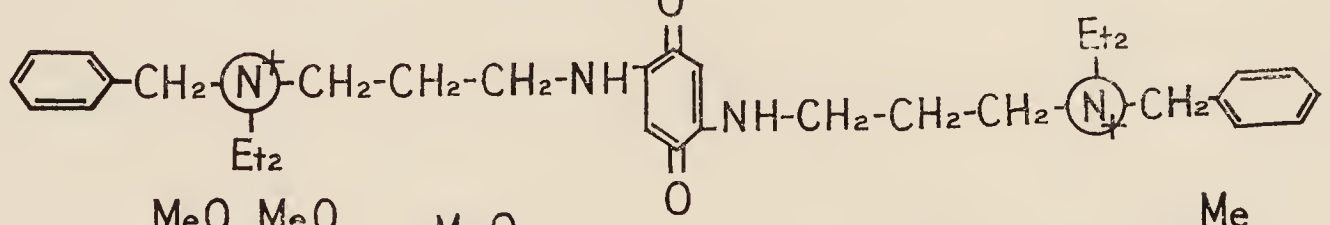
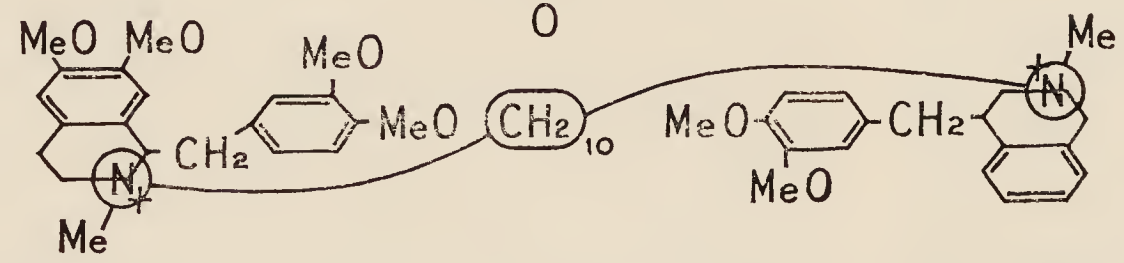
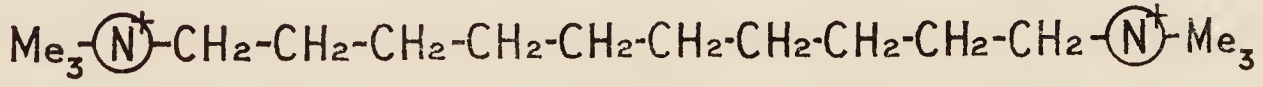
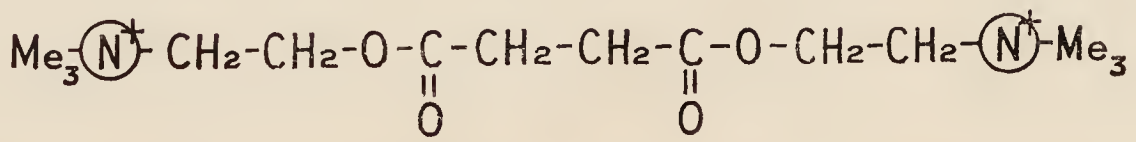
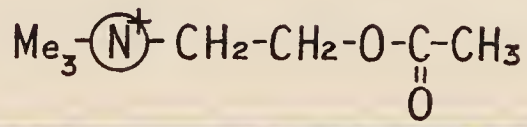
Relation of Structure to Action

No one yet knows what property it is that confers neuromuscular blocking action on a molecule, and it is difficult to discuss it profitably. Some of the important factors may however be mentioned briefly:

1. *The terminal group.*—It seems clear that quaternary nitrogen provides far the richest quarry for neuromuscular blocking agents. This discovery, now nearly a hundred years old, is one of the classic steps in pharmacology. The work of Crum Brown and Fraser, showing that a wide range of natural alkaloids (including morphine, atropine and strychnine) after quaternisation lost their normal highly diverse actions and came to produce a single action, that of neuromuscular block, represents the first correlation of chemical structure with pharmacological action. It is fascinating to read their account of tests on rabbits paralleling exactly the modern head-drop test, and to find them applying their theories to the synthesis of the first artificial neuromuscular blocking agent, tetramethylammonium iodide, in the hope of obtaining a therapeutically useful agent " readily obtained in a state of constant purity and therefore of constant strength ".

In those compounds which possess a depolarising action, it seems important that their terminal groups should remain methylated, as they are in acetylcholine. Conversion of more than one of these to ethyl changes the compound first to a mixed and then to a competitive drug.

2. *Interquaternary distance.*—The general theory that a distance corresponding to 8–12 carbon atoms between two quaternary groups favours neuromuscular activity, has proved successful: and all compounds now in use can be regarded as conforming more or less to this pattern. (v. Table II). There is no established reason for this: the plausible and obvious explanation, that this distance corresponds to the distance between receptor sites at the endplate, is still purely speculative.

Compound	*Structure*	*Approximate Dose in Man mg/kg*	*Approximate Duration of Action (mins)*	*Special Features*
Competitive Blocking Agents				
D-tubocurarine ...		0.2	20–30	Ganglionic block Histamine release
Gallamine		0.7	15–30	Tachycardia
Dimethylether of d.t.c	As d-tubocurarine with MeO- instead of OH-	0.06	20–25	
Mytolon		0.2	15–20	Anticholinesterase activity
Laudolissin		0.2	25–35	Histamine release
Depolarising Blocking Agents				
Decamethonium ...		0.035	10–20	Action varies inversely with blood flow
Succinylcholine ...		0.15 +	3–5	Stimulation of ganglia Histamine release
Acetylcholine ...				

3. *The nature of the molecular skeleton.*—A bare aliphatic scaffolding, as in decamethonium, seems to favour depolarising action whereas a well-upholstered molecule (such as d-tubocurarine) is more likely to be competitive. Bovet has gone so far as to suggest that such drugs should be classified as "lepto-" and "pachy-curares"; but there are sufficient exceptions (*e.g.*, nicotine, a depolarising drug with a fairly plump molecule) to make it difficult to press the generalisation so far.

The Testing of Muscle Relaxants in Animals and Man

The increasing precision both of animal experimentation and of clinical work has made it more and more difficult to predict, by extrapolation from experiments in animals, the required details of the behaviour of a muscle relaxant in clinical use. The main doubt in the initial pharmacological work to cover these points is as to the most suitable animal for them. In many ways the cat is best; it has, thus far, yielded the most reliable estimates of absolute potency in man and of modes of action. It is, in addition, unrivalled for studies on the blood-pressure, on ganglionic effects, and on histamine release. But there is no doubt that at present tests should be conducted on several species in building the pharmacological background of a new relaxant.

The limitations of animal work have led to the development by many workers of methods for assessing muscle relaxants on human subjects before their full clinical use. This offers many advantages, especially that a vivisection licence may be dispensed with; and information on the mode of action can often be obtained (c.f. Table I). A real dilemma arises, however, at this point. In the first place, the test can be on unanæsthetised subjects, using some convenient muscle, usually those of the hand, as the test object. Several difficulties arise with such a test. The feelings of the subject during the experiment cannot altogether be neglected; and sometimes at any rate there is distinct tachycardia and hypertension, indicating an autonomic activity which might well interfere with the assessment of the test. Further, one is uncertain that the proprioceptive discharges in the conscious individual correspond at all to that of the anæsthetised subject; yet clearly these will be of great importance in maintaining the tone which muscle relaxants are used to abolish. Third, the hand and its muscles are highly specialised structures, with functions widely different from the musculature of trunk and abdomen, and certainly more sensitive to d-tubocurarine than the latter.

On the other hand one may try to assess the effectiveness of a relaxant under conditions identical with those of normal use. For general surgical operation, this would require an instrument for measuring the relaxation of the abdominal muscles, or of whatever other muscles are concerned. No such instrument has yet been developed and the effectiveness of relaxation is judged more by the

placidity of the surgeon than anything else. Some attempts have been made in electro-convulsion therapy to develop a scoring system graded according to the intensity of a convulsion, and so to compare (for instance) the depression of the vital capacity or the respiratory minute volume just before convulsions mitigated to an equal degree by two different drugs. This is a relatively crude method, but has the over-riding advantage of studying the two things which are of primary interest—the attenuation of the convulsion and the reduction of respiratory movement. It would be a major advance if a similar objective scoring system to estimate abdominal relaxation could also be developed.

Special Features of Certain Relaxant Drugs (Table II)

(*a*) *D-tubocurarine.*—The mode of action of this, the classical drug for the production of neuromuscular block, has been discussed. Of the principal additional actions of d-tubocurarine (ganglion-block, histamine release, and stimulation of the C.N.S.) that of ganglion block requires more attention. Its potency in this respect is not very far short of its activity at the neuromuscular junction and is of the same competitive character. It tends to be directed particularly at parasympathetic ganglia, in animals at least. There seems to be no unanimity as to whether this ganglionic-blocking power is an asset or a liability. The clinical impression exists that it tends to diminish the fluctuations of blood pressure produced, for instance, in surgical manipulations of the viscera; but there is no decisive evidence on the point. The association of ganglion-blocking with neuromuscular blocking activity is probably chiefly to be deplored because they cannot be controlled independently. If ganglionic block were deliberately sought, it seems more rational to use a neuromuscular blocking agent free of ganglionic action together with a specific ganglionic blocking agent.

(*b*) *Gallamine.*—The low potency of gallamine (flaxedil, 2559F, RP3697) compared to other relaxants serves as a reminder that it is not potency *per se* but potency in relation to other toxicity, that determines the safety of the drug. The main peculiarity of gallamine is the tachycardia it produces. This is an effect specifically exerted on the cardiac branches of the vagus nerve; it resembles an atropine effect, in that it prevents also the bradycardia produced by injected acetyl-β-methylcholine; but it is anomalous in that the atropine-like effect is seen *only* on the heart-rate, and not on other structures such as blood-vessels, eyes, or salivary glands. There is no real analogy to this intensely selective blocking action, and it remains a pharmacological puzzle. The general clinical impression that it is harmless except where the tachycardia itself might be dangerous seems in accord with pharmacological experience.

(*c*) *Mytolon.*—This compound is fundamentally d-tubocurarine-like, but it presents certain novel features; it is coloured a cheerful reddish-orange tint, and it is (unexpectedly) a benzoquinone derivative.

More important to the clinician, it has a considerable anticholinesterase activity (about $\frac{1}{4}$ that of neostigmine against the dog's red cell cholinesterase). With this latter property may well be associated certain pharmacological properties normally associated with depolarising drugs (such as the insensitivity of the rat, the poor antagonism to it by anticholinesterases, the partial sustaining of a tetanus, and perhaps a tendency to produce a particular type of diaphragmatic respiration). It also causes the side effects of salivation, colic, bradycardia, occasional extra-systoles, and rarely bronchospasm; the salivation is the most troublesome feature with unanæsthetised subjects, and can only be fully controlled with atropine when the dose of Mytolon given is not big. It has some histamine-liberating activity.

(*d*) *Decamethonium*.—The main actions of decamethonium have already been described. An important additional observation on the action of decamethonium was made by Churchill-Davidson & Richardson, when they showed that the intensity of its action varied inversely with the blood flow through the part concerned. Thus it was very difficult to paralyse a hand in which vasomotor tone had been removed by nerve-block; but paralysis was exceptionally intense and prolonged when the blood flow to the limb was lessened.

This work has not been extended to other blocking agents. But it may serve to elucidate many details of behaviour of the relaxants, particularly when their duration of action is unusual. A prolonged effect by a relaxant, for instance, might sometimes be due not so much to hypersensitivity, nor to delayed excretion, but simply to an ischemia of the region involved.

(*e*) *Succinylcholine*.—This compound produces neuromuscular block by direct depolarisation of the endplate. The suggestion has been made that it may act indirectly through the inactivation of the cholinesterase; but there is no evidence for this. It is known to depolarise muscle directly; for instance a dose of 2 μg injected into a cat's tibialis produced a substantial reduction of membrane potential, although in the same preparation 0.5 mg. neostigmine had no depolarising action. It elicits contractures of avian and frog muscle in the same fashion as does decamethonium, but not in the way that anticholinesterases do. It is in any case only a weak anticholinesterase. In man it promptly produces fasciculations, just as does decamethonium, but somewhat more vigorously.

An important characteristic is its susceptibility to the blood cholinesterase in man. To this is due its great brevity of action. Occasional instances of hypersensitivity have been reported, and the evidence is suggestive that in such patients the cholinesterase is reduced considerably below normal levels. The injection of a purified cholinesterase preparation will shorten the action of succinylcholine; for instance if the plasma cholinesterase content is doubled by such an injection, the duration of apnœa from an injection of succinylcholine is approximately halved.

The brevity of action of the drug has led to its use in a novel way, by continuous infusion. This offers the advantage that a very accurate control of depth of relaxation can be obtained, and that when required rapid return to normal can be obtained by stopping the infusion. But this technique, because it allows relatively large total quantities to be given, forces reconsideration of two pharmacological points. First, it is possible that products of hydrolysis may be active. With single injections only negligible quantities of succinylmonocholine or of choline will be released; but with prolonged infusion large amounts will accumulate, particularly the former if the second choline group is split away more slowly than the first (as has been observed with related compounds). Choline itself can affect the cat's neuromuscular junction in a dose corresponding to that obtainable from about ½–1 gm. of succinylcholine in man. Accumulation of the monocholine or choline itself may account for the prolonged action of succinylcholine sometimes observed.

Second, the large doses produce side effects negligible with a single dose of succinylcholine. Three actions may be seen:

1. A small muscarine-like transient fall of blood pressure which may be produced either by succinyldicholine or the monocholine, or possibly even choline itself.

2. If atropine has been administered, the muscarine effect is abolished and stimulation of vasomotor ganglia occurs with resulting rise of blood pressure. Both succinylcholine and its monocholine derivative exert this action. This may be the cause of the continued rise in blood pressure sometimes seen in anæsthetic use.

3. In large doses succinylcholine can release histamine, although it is much less liable to do so than, say, d-tubocurarine. Since, however, doses 50 times greater may be given than are given of the latter drug, even a comparatively slight activity of this sort may be of importance.

Nomenclature

Many terms are bandied about in reference to neuromuscular block. In this review an attempt has been made to use only certain terms to which a precise meaning can be attached. The terms " depolarising " and " competitive " are in this respect fairly satisfactory. The term " curare-like " could also be useful in that way, since all the natural alkaloids isolated from preparations of curare so far act in a way similar to d-tubocurarine. On the other hand, it is also true that all the muscle relaxants have a curare-like aspect, in that they do not interfere with nervous transmission, do not prevent contraction of the muscle and do not prevent acetylcholine release. Further, it is possible that eventually a depolarising drug will be isolated from a curare preparation, as it has already been isolated, in the form of tetra-methylammonium salt, from the Sudanese plant *Courbonia virgata A Prongn.* It is probably, therefore, wiser to avoid

the term " curare-like " except as a general phrase to describe a particular group of muscle relaxants to be distinguished from such things as mephenesin.

Another term occasionally met with is that of " substitution " rather than " competition ". The use of this term suggests a misunderstanding of the dynamic processes which must underlie neuromuscular block. It is not now supposed that, for instance, d-tubocurarine molecules come to be glued firmly to the surface of a muscle membrane, thereby preventing acetylcholine molecules from resting there. But it is rather believed that there is a continuous flux in which acetylcholine and curare repeatedly make and break their unions with the receptor groups; so that the proportion of receptor groups filled at a given instant by curare molecules will depend on the relative rates at which acetylcholine and the competing drug combine with and break away from them. The molecules are thus constantly and actively competing with each other, and are not in a fixed state with molecules firmly and permanently attached to the membrane. The term " substitution " hardly conveys this dynamic picture and leads to difficulties in thinking of how the process of block passes off.

Conclusion

A review of the pharmacological principles of the use of neuromuscular blocking agents outlined above suggests two concluding comments. First, an important pharmacological principle (usually expressed in terms of the ratio of toxic dose to therapeutic dose) has not been stated: that a patient should not be subjected to a therapeutic agent unless the increased safety or welfare from its use outweighs the increased danger it brings. The intrinsic interest of neuromuscular paralysis, of human reactions to drugs producing it, and of developing new drugs, and the great surgical help that relaxants provide, have drawn attention and effort away from the problem of assessing how far assisted or completely controlled respiration deviates from the physiological, and how important such deviations are in the different types of case which now receive relaxants. This is partly a problem of respiratory physiology, partly a problem of records and statistical analysis. But the pharmacologist as much as the anæsthetist must hope that the interest developing in this field will bear fruit before the development of new pharmacological agents outstrips too far their clinical justification.

Second, one gains the impression from the current literature that relaxants come and go rather easily and are accepted or rejected on relatively slight grounds. Yet among those available, when one considers the pharmacological knowledge gained about them, there must be many differences which could be usefully exploited if only they could be assessed properly in practice. The major requirement in the field of muscle relaxants is perhaps not more relaxants, but the development of methods for assessing and properly exploiting those we have.

GLOSSARY

Action Potential.—The transient electrical potential which can be measured between two points on a nerve or muscle fibre during propagated activity. Its sign is such that the active membrane becomes negative to resting membrane. The rapid part is often referred to as a " spike potential ".

Anode.—Of a pair of electrodes, the positive one.

Cathode.—Of a pair of electrodes, the negative one, at which excitation normally takes place, with brief shocks.

Competitive Antagonism.—A type of antagonism of one drug to another in which it is believed that they compete with each other for the same receptors. Typically, (1) the action of an excitant drug is depressed by another of similar chemical constitution but itself not excitant; (2) the antagonism is reversible; (3) the antagonism can be overcome by increasing the concentration of stimulant drug, and the intensity of the antagonism depends *approximately* on the ratio of concentration of the two drugs present.

Contraction.—The muscular response which is associated with the passage of an action potential and contraction wave down a muscle fibre.

Contracture.—The slow shortening of a muscle, localised to a particular region, with which there is no propagated electrical or mechanical activity.

Curare.—One of 20–30 spellings of the South American Indian's name for certain complex vegetable arrow-poisons, acting chiefly through neuromuscular block.

Curare-like: Curarising: Curariform.—Terms signifying a vague and too often unspecified relationship to one of the curare alkaloids. It might be used to refer to neuromuscular blocking agents as a whole group; or to those whose action resembles that of the natural alkaloids. But its use retains a danger of confusion.

Depolarisation.—The removing by injury, by electrical currents, or by drugs of the electric charge normally present across an excitable membrane.

Endplate.—This may refer to one or several of three structures: (*a*) the terminal arborisations of the motor nerve, often extremely elaborate and forming a plaque-like structure. This is better referred to as the nerve-ending; (*b*) the glial cellular structures surrounding the nerve-ending; (*c*) that part of the muscle fibre membrane lying immediately under the nerve-ending, which is histologically differentiated from the rest of the muscle membrane, the so-called " palisade " structure. It is probably here that the specific reaction with acetylcholine occurs, and in this review it is referred to as the " endplate itself ".

Endplate Potential.—The transient non-propagated local negativity which may be detected at the end-plate region after motor nerve stimulation in the curarised muscle.

Endplate Region.—Comprises the endplate itself together with the adjacent muscle membrane which may be depolarised by local current spread from the endplate.

Fasciculation.—Incoordinate contractions of relatively large groups of muscle fibres, probably in motor units, often produced by the administration of a drug which depolarises the motor endplate.

Fibrillation.—The completely incoordinate spontaneous activity of individual muscle fibres, which follows denervation of a muscle.

Nerve-Ending.—Often loosely used to refer not only to the termination of the motor nerve but also to the surrounding structures and the muscle membrane with which the nerve ending comes into relation. It is a term best confined to the actual terminations of the nerve itself. It is perhaps legitimate (though confusing) to say that d-tubocurarine acts *at* the nerve-endings; it is wrong to say that d-tubocurarine acts *on* them.

Membrane.—The structure limiting the interior of a nerve or muscle fibre, across which the membrane potential may be recorded, and damage to which produces an injury-potential. It is to be distinguished from, *e.g.*, fascial sheaths.

Onium Salts.—Positively charged cations of the ammonium, phosphonium sulphonium type, in which the central atom satisfies its maximum covalency with carbon radicals, and as a result exerts one electrovalency as well.

Polarisation.—(see also Depolarisation). The establishing or existence of a potential difference across a membrane or interface.

Propagation.—The setting-up and passage of an action potential along an excitable structure. The propagation threshold at the endplate is that depolarisation of the membrane adjacent to the endplate which will just enable the membrane response associated with propagated action potentials to be initiated.

Receptors.—Purely hypothetical entities conjured up by pharmacologists to explain the action of drugs. It is postulated that they combine with the drugs in a way analogous to the reactions of which the drugs are capable chemically in the test tube.

References

Detailed references have deliberately been omitted. They can mostly be found in the Curare Symposium in the Annals of the N.Y. Academy of Sciences (1951); in Pharmacological Reviews by C. C. Hunt and S. W. Kuffler (1950), and by W. D. M. Paton and E. J. Zaimis (1952); in papers by A. L. Hodgkin, A. F. Huxley, and B. Katz in the Journal of Physiology (1945–1953); and in recent papers in the pharmacological and clinical journals.

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